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Left Atrial Function Predicts Heart Failure Hospitalization in Subjects With Preserved Ejection Fraction and Coronary Heart Disease

Longitudinal Data From the Heart and Soul Study

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Objectives This study sought to determine whether left atrial (LA) dysfunction predicts heart failure (HF) hospitalization in subjects with preserved baseline ejection fraction (EF).

Background Among patients with preserved EF, factors leading to HF are not fully understood. Cross-sectional studies have demonstrated LA dysfunction at the time of HF, but longitudinal data on antecedent atrial function are lacking.

Methods We performed resting transthoracic echocardiography in 855 subjects with coronary heart disease and EF ≥50%. Left atrial functional index (LAFI) was calculated as ([LA emptying fraction × left ventricular outflow tract-velocity time integral] / [indexed LA end-systolic volume]), where LA emptying fraction was defined as (LA end-systolic volume − LA end-diastolic volume) / LA end-systolic volume. We used Cox models to evaluate the association between LAFI and HF hospitalization.

Results Over a median follow-up of 7.9 years, 106 participants (12.4%) were hospitalized for HF. Rates of HF hospitalization were inversely proportional to quartile (Q) of LAFI: Q1, 47 per 1,000 person-years; Q2, 18.3; Q3, 9.6; and Q4, 5.3 ($p < 0.001$). Each standard deviation decrease in LAFI was associated with a 2.6-fold increased hazard of adverse cardiovascular outcomes (unadjusted hazard ratio: 2.6, 95% confidence interval: 2.1 to 3.3, $p < 0.001$), and the association persisted even after adjustment for clinical risk factors, N-terminal pro–B-type natriuretic peptide, and a wide range of echocardiographic parameters (adjusted hazard ratio: 1.5, 95% confidence interval: 1.0 to 2.1, $p = 0.05$).

Conclusions Left atrial dysfunction independently predicts HF hospitalization in subjects with coronary heart disease and preserved baseline EF. The LAFI may be useful for HF risk stratification, and LA dysfunction may be a potential therapeutic target. (J Am Coll Cardiol 2012;59:673–80) © 2012 by the American College of Cardiology Foundation

Heart failure (HF) is a major public health problem, affecting 5.8 million people in the United States, with estimated direct and indirect costs of $39 billion in 2010 (1). Heart failure is the number 1 cause of hospitalization in persons over the age of 65 years (2), and approximately one-half of all HF hospitalizations occur in patients who have HF with preserved ejection fraction (HFpEF) (3,4). Patients with HFpEF have increased mortality and morbidity, similar to that of patients with HF and reduced EF (5,6). Although medical and device therapies have improved survival for patients with low EF, large randomized trials of traditional HF therapies such as angiotensin-blockade have not demonstrated a survival benefit in HFpEF (7–9). The underlying pathophysiology of HFpEF is complex (10), and factors precipitating HF events in patients with preserved EF are not well understood (11).

Classically, HFpEF has been attributed to diastolic dysfunction and left ventricular (LV) stiffness, resulting in

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Abbreviations and Acronyms

AF = atrial fibrillation/flutter
CI = confidence interval
E/A ratio = ratio of early rapid filling to late atrial contraction
EF = ejection fraction
HF = heart failure
HFpEF = heart failure with preserved ejection fraction
HR = hazard ratio
LA = left atrial/atrium
LAFI = left atrial functional index
LAVI = left atrial volume index
LV = left ventricle/ventricular
NT-proBNP = N-terminal pro–B-type natriuretic peptide
PASP = pulmonary artery systolic pressure
VTI = velocity time integral

elevated LV end-diastolic pressures (12). However, diastolic dysfunction and LV hypertrophy are also common in patients with hypertension, many of whom never have clinical HF (13,14). Therefore, additional discriminating features to identify subjects at highest risk of HF development are of interest both from a clinical and from a pathophysiologic standpoint.

Left atrial (LA) remodeling due to overt or subclinical atrial volume or pressure overload could result in decreased atrial systolic function. Atrial dysfunction could lead to impaired atrial emptying, which decreases cardiac output, or it could be an early indicator of cardiac congestion or failure even when EF is preserved. Cross-sectional studies have demonstrated an association between LA dysfunction and HFpEF (14), but longitudinal studies to assess whether LA dysfunction predicts future HF events are lacking. Therefore, we evaluated the longitudinal association of LA function, as assessed by the left atrial functional index (LAFI), to HF hospitalization in subjects with prevalent coronary heart disease and preserved baseline EF.

Methods

Participants. The Heart and Soul Study is a prospective cohort study originally designed to investigate psychosocial factors and health outcomes in patients with stable coronary heart disease. Details regarding recruitment methods and study design have been previously published (15). Briefly, between September 2000 and December 2002, we recruited 1,024 out-patients with stable coronary heart disease from 2 Veterans Administration Medical Centers (Palo Alto and San Francisco), 1 university medical center (University of California, San Francisco), and 9 public health clinics in the Community Health Network of San Francisco. Eligible participants met 1 or more of the following criteria: 1) history of myocardial infarction; 2) evidence of at least 50% stenosis in 1 or more coronary vessels on cardiac catheterization; 3) evidence of exercise-induced ischemia by treadmill electrocardiogram or nuclear perfusion stress imaging; or 4) a history of coronary revascularization. We excluded subjects with a history of myocardial infarction in the previous 6 months, inability to walk 1 block, or planning to move out of the local area within 3 years.

Of the 1,024 original study subjects, we excluded the following participants: 110 with baseline EF <50%, 15 with moderate or greater valvular disease, 40 with missing echocardiographic data, and 4 lost to follow-up. The remaining 855 participants are the subjects of this analysis. This study was approved by the institutional review board, and all participants provided written, informed consent.

Measurements. PREDICTOR VARIABLE, LEFT ATRIAL FUNCTION INDEX. We performed resting transthoracic echocardiography in 855 participants with coronary heart disease and preserved EF (≥50%). These studies were performed in the standard left lateral recumbent and supine positions using an Acuson Sequoia ultrasound system (Siemens Medical Solutions, Mountain View, California). We obtained standard 2-dimensional parasternal short-axis and apical 2- and 4-chamber views during held inspiration, and planimetered these with a computerized digitization system to determine end-diastolic and end-systolic LV volumes by the biplane method of disks. The moments of first mitral valve opening and closing were used to determine end-diastolic and end-systolic LV volumes.

The derivation and validation of the LAFI has been previously described (16). The LAFI was calculated as: ([LA emptying fraction × LV outflow tract-velocity time integral (VTI)] / [LA end-systolic volume index)], where LA emptying fraction was defined as: (LA end systolic volume − LA end-diastolic volume) / LA end-systolic volume (Fig. 1). All echocardiograms were performed using a standardized protocol by 1 of 2 trained and experienced technicians.

A single experienced reader blinded to clinical information (N.B.S.) interpreted all studies and verified the measurements used for the calculation of LAFI. The reproducibility of LAFI by this reader has been previously described with Bland-Altman analyses, which revealed no significant variation (intraobserver reproducibility: mean difference 0.0059, 95% confidence interval [CI]: 0.015 to −0.012; interobserver reproducibility: mean difference 0.0017, 95% CI: 0.025 to −0.013) (16).

OUTCOME VARIABLE, HF HOSPITALIZATION. The primary outcome was time to first HF hospitalization. We conducted annual follow-up interviews with participants or their proxy to inquire about interval hospitalization for "heart trouble." For any reported event, we retrieved medical records, which 2 independent and blinded physician adjudicators reviewed. If the adjudicators agreed on the outcome classification, their classification was binding. In the event of a disagreement, a third blinded adjudicator was consulted.

We defined HF as hospitalization for a clinical syndrome based on the Framingham congestive HF criteria, which require validation of 2 major or 1 major plus 2 minor criteria. Major criteria are paroxysmal nocturnal dyspnea, orthopnea, elevated jugular venous pressure, pulmonary rales, third heart sound, cardiomegaly on chest radiograph, pulmonary edema on chest radiograph,

$$\text{LAFI} = \frac{\text{LA emptying fraction} \times \text{LVOT VTI (cm)}}{\text{LAESV indexed to BSA (cc/m}^2\text{)}}$$

LAFI units = (cm) x (m^2)/cc (i.e. units cancel out)
LVOT VTI = velocity time integral of the left ventricular outflow tract (cm)
LAESV = maximal left atrial volume in end systole (cc)
BSA = body surface area

Figure 1 **Derivation of the LAFI**

The left atrial functional index (LAFI) is an index of atrial function that incorporates analogues of cardiac output (left ventricular outflow tract [LVOT] velocity time integral [VTI]), atrial reservoir function (left atrial emptying fraction) and indexed atrial size (maximal left atrial volume in end systole [LAESV]). The LAFI, therefore, provides a simple echocardiographic measure of left atrial function that extends information from chamber volume by accounting for physiologic influences that include stroke volume, reservoir function, and body habitus. BSA = body surface area.

weight loss ≥4.5 kg in 5 days in response to HF therapy; minor criteria are peripheral edema, night cough, dyspnea on exertion, hepatomegaly, pleural effusion, heart rate >120 beats/min (13,17).

OTHER MEASUREMENTS. Age, sex, race, and medical history (including history of HF) were determined by self-reported questionnaire. We measured height and weight, and calculated body mass index (kg/m^2). Systolic blood pressure, diastolic blood pressure, and heart rate were measured in the supine position after 5 min of rest. We measured serum creatinine, low-density lipoprotein, high-density lipoprotein, and N-terminal pro–B-type natriuretic peptide (NT-proBNP) from fasting blood samples drawn at the baseline study appointment. Estimated glomerular function was calculated by the abbreviated (4-variable) Modification of Diet and Renal Disease Study formula, as follows: estimated GFR = 186 × (serum creatinine$^{-1.154}$) × (age$^{-0.203}$) × (0.742 if female) × (1.21 if black) (18). We performed standard 12-lead electrocardiograms on all subjects at the time of enrollment and again after 5 years of follow-up. Two independent, blinded physicians adjudicated the rhythm of all electrocardiograms. In the event of a disagreement, a third adjudicator was consulted.

From the resting echocardiograms, the left atrial volume index (LAVI) was defined as LA end-systolic volume divided by body surface area. The LVEF was calculated as (end-diastolic volume minus end-systolic volume) divided by end-diastolic volume (19). The LV mass was calculated using the truncated-ellipse method (20) and indexed to body surface area. We defined 3 categories of diastolic dysfunction on the basis of mitral flow ratios of peak velocities at early rapid filling and late filling at atrial contraction (E/A ratio) and systolic or diastolic dominant pulmonary venous flow: 1) impaired relaxation, defined as an E/A ratio of 0.75 or less and systolic dominant pulmonary venous flow; 2) pseudonormal, defined as an E/A of 0.75 to 1.5 and diastolic dominant pulmonary venous flow; and 3) restrictive, defined as an E/A of 1.5 or greater and diastolic dominant pulmonary venous flow (13). We have previously found differences in rates of cardiovascular outcomes in these 3 categories of diastolic dysfunction (no diastolic dysfunction, impaired relaxation, pseudonormal/restrictive) (21); therefore, we analyzed diastolic dysfunction as an ordinal variable at these 3 levels. Because <5% of the study sample had restrictive filling, the pseudonormal and restrictive groups were combined for analysis.

To determine presence of inducible ischemia at baseline, all participants underwent exercise treadmill testing according to a standard Bruce protocol with continuous 12-lead electrocardiogram monitoring. We performed echocardiography immediately before and after exercise. We defined inducible ischemia as the presence of ≥1 new wall motion abnormality at peak exercise.

We estimated pulmonary artery systolic pressure (PASP) from echocardiography as tricuspid regurgitation gradient plus right atrial pressure. The tricuspid regurgitation jet was visualized with color flow mapping, and the tricuspid regurgitation gradient was measured with continuous-wave Doppler. We used the modified Bernoulli equation (delta P = $4v^2$) to calculate gradients from velocities. Right atrial pressure was estimated from the size and respiratory variation of flow in the inferior vena cava.

Statistical analysis. Participants were divided into quartiles based on their LAFI. We compared differences in baseline characteristics across quartiles using chi-square tests for categorical variables and 1-way analysis of variance for continuous variables. Cumulative event-free survival was measured by the method of Kaplan-Meier, and unadjusted differences were compared using the log-rank test. We performed multivariate Cox regression to compare the rate of HF hospitalization across quartiles of LAFI. To determine the independent prognostic value of LAFI, we used incremental multivariate models adjusting for covariates demonstrating an association with LAFI at $p \leq 0.1$. We adjusted for age, sex, and race (model 1); plus tobacco use, prior revascularization, history of HF, atrial fibrillation, estimated glomerular filtration rate, low-density lipoprotein cholesterol, angiotensin inhibitors, loop diuretics, and resting heart rate

(model 2); plus baseline inducible ischemia (model 3); plus NT-proBNP (model 4); plus diastolic dysfunction, left atrial volume index, left ventricular ejection fraction, and left ventricular mass index (model 5). Using the same models, we also examined the rate of HF hospitalization using per SD decrease in LAFI.

Most echocardiographic measures were complete or near complete in all subjects, with the exception of PASP (missing data: left ventricular ejection fraction [n = 0], left atrial volume index [n = 0], left ventricular mass index [n = 6], and diastolic dysfunction [n = 19]; PASP [n = 396]). To determine whether the missing data for PASP was informative, we created a 5-category variable (PASP in quartile 1, 2, 3, 4, or missing) and entered this as an indicator variable. We then tested for interaction to determine whether the association between LAFI and HF differed by age, sex, diabetes, hypertension, obesity, AF, or history of HF, with a cut-off of $p \leq 0.1$ considered statistically significant. We also performed a sensitivity analysis in which we adjusted for interim myocardial infarction and AF as time-varying covariates to determine whether the association was independent of interval development of cardiac events. Assessment of assumption of proportional hazards using log-minus-log curves and the Schoenfeld test revealed no violations (22,23).

We have previously found that LV outflow tract–VTI (24) and LAVI (25), 2 of the component measures used to derive LAFI, predict HF hospitalization in this cohort. Therefore, we used c-statistics and chi-square likelihood ratio testing to compare the discrimination of LAFI with each of its individual components. Our group has also found NT-proBNP to be a powerful predictor of HF hospitalization in this cohort (26); therefore, we also compared the discrimination of LAFI with NT-proBNP, which was log-transformed to meet the assumption of linearity. Correlated c-statistics were performed using proportional haz-

Table 1 Baseline Characteristics of 855 Participants With Stable Coronary Heart Disease and Ejection Fraction ≥50%, by Quartile of Left Atrial Functional Index

	Quartile I (0.5–29.2 U) (n = 214)	Quartile II (29.3–40.8 U) (n = 214)	Quartile III (40.8–53.4 U) (n = 214)	Quartile IV (53.4–160 U) (n = 213)	p Value
Demographics					
Age, yrs	70.0 ± 10.1	65.6 ± 10.9	65.5 ± 10.3	64.9 ± 11.1	<0.001
Male, %	84.1	82.2	79.0	77.5	0.29
Caucasian, %	68.2	55.6	60.3	53.3	0.01
Medical history					
MI	51.2	52.4	47.2	54.0	0.54
CHF	25.4	11.4	9.9	11.3	<0.001
Hypertension	77.9	81.2	74.8	80.3	0.37
Diabetes mellitus	26.2	27.4	31.3	27.2	0.65
Stroke/TIA	15.4	14.2	10.8	12.7	0.54
Atrial fibrillation	16.4	0.5	0.5	0.0	<0.001
Revascularization	63.9	60.9	55.1	51.6	0.05
Angina	59.2	62.7	58.4	61.5	0.78
Obesity*	27.6	34.6	36.0	35.7	0.21
Current tobacco use	13.6	20.8	19.3	23.9	0.05
Laboratory					
HDL, mg/dl	46.2 ± 13.9	44.9 ± 14.1	46.4 ± 14.3	46.3 ± 13.4	0.63
LDL, mg/dl	99.6 ± 32.0	102.9 ± 34.2	106.5 ± 33.2	107.4 ± 32.3	0.07
eGFR,† mg/dl	71.8 ± 23.5	78.7 ± 22.4	79.8 ± 23.4	77.3 ± 22.0	0.001
Log NT-proBNP	5.9 ± 1.2	5.0 ± 1.2	4.8 ± 1.0	4.5 ± 1.1	<0.001
Medication use					
Aspirin	72.4	81.3	79.4	79.3	0.13
Beta-blocker	62.2	59.4	56.5	52.6	0.22
Angiotensin-converting enzyme inhibitor	55.6	50.0	49.1	40.9	0.02
Statin	65.9	63.1	66.8	59.2	0.35
Loop	20.1	12.2	7.9	12.7	0.003
Thiazide	15.9	11.7	15.0	16.9	0.46
Hemodynamics					
SBP, mm Hg	135 ± 21	134 ± 22	134 ± 23	132 ± 18	0.60
DBP, mm Hg	75 ± 12	75 ± 11	75 ± 11	75 ± 11	0.93
Pulse pressure, mm Hg	60 ± 16	59 ± 17	59 ± 18	57 ± 15	0.20
Heart rate, beats/min	66.1 ± 12.9	66.9 ± 11.2	67.8 ± 11.9	69.0 ± 11.6	0.08

Values are mean ± SD or %. *Defined as body mass index ≥30 kg/m^2. †Estimated glomerular filtration rate (eGFR) by Modification of Diet in Renal Disease equation.

CHF = congestive heart failure; DBP = diastolic blood pressure; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MI = myocardial infarction; NT-proBNP = N-terminal pro–B-type natriuretic peptide; SBP = systolic blood pressure; TIA = transient ischemic attack.

Table 2 Baseline Measures of Other Known Prognostic Markers by Quartile of Left Atrial Functional Index Among 855 Participants With Coronary Heart Disease and Ejection Fraction ≥50%

	Quartile I (0.5–29.2 U) (n = 214)	Quartile II (29.3–40.8 U) (n = 214)	Quartile III (40.8–53.4 U) (n = 214)	Quartile IV (53.4–160 U) (n = 213)	p Value
LV mass index, g/m^2	196 ± 56	189 ± 51	180 ± 50	172 ± 48	<0.001
LVEF, %	61.6	63.8	65.4	66.7	<0.001
LAVI, ml/m^2	43.0 ± 13.5	32.6 ± 6.7	29.3 ± 6.8	23.8 ± 5.7	<0.001
Diastolic dysfunction					
None	41.6	63.1	62.6	67.6	<0.001
Impaired relaxation	21.0	20.1	24.3	19.7	0.65
Pseudonormal/restrictive	16.8	8.4	7.0	5.2	<0.001
PASP, mm Hg	32.0 ± 8.4	29.8 ± 6.9	30.9 ± 9.8	28.2 ± 5.9	0.002
Inducible ischemia	28.7	21.6	18.3	17.0	0.02
Log NT-proBNP, pg/ml	5.9 ± 1.2	5.0 ± 1.2	4.8 ± 1.0	4.5 ± 1.1	<0.001

Values are mean ± SD or %.
LAVI = left atrial volume index; LV = left ventricle; LVEF = left ventricular ejection fraction; PASP = pulmonary artery systolic pressure.

ards models with post-estimation commands. All analyses were conducted using STATA (version 11.0, StataCorp, College Station, Texas).

Results

During a median follow-up of 7.9 years (interquartile range: 4.8 to 8.1 years), 106 subjects (12.4%) were hospitalized for HF, of whom 71 (67.0%) had no prior history of HF. Baseline characteristics of participants across quartiles of LAFI are displayed in Table 1. The LAFI was also strongly associated with each of the other prognostic biomarkers and echocardiographic parameters (Table 2).

Event rates increased from 5.3 per 1,000 person-years in the highest quartile of LAFI to 47.0 per 1,000 person-years in the lowest quartile (Table 3). Kaplan-Meier survival estimates (Fig. 2) revealed early separation of the event-free survival curves (within the first few months), which continued to diverge throughout follow-up. After adjustment for demographics (age, sex, white race), clinical risk factors (tobacco use, prior revascularization, history of HF, AF, low-density lipoprotein, estimated glomerular filtration rate) medication use (angiotensin inhibitors, loop diuretics), and heart rate, every SD decrease in LAFI increased the adjusted hazard of HF 2-fold (HR: 2.0, 95% CI: 1.5 to 2.7; $p < 0.001$). The association also remained independent after further adjustment for log NT-proBNP and a wide range of other echocardiographic measures (per SD decrease in LAFI, HR: 1.5, 95% CI: 1.0 to 2.1; $p = 0.05$). Even after further adjustment for pulmonary artery systolic pressure, point estimates revealed little attenuation (per SD decrease in LAFI, HR: 1.4, 95% CI: 0.9 to 2.1; $p = 0.10$) (Table 4). Notably, when PASP was entered into the model as a categorical predictor with missing data treated as a fifth category, data from the missing category was noninformative with respect to the association between LAFI and HF (HR: 0.88, 95% CI: 0.4 to 1.9, $p = 0.88$).

To determine whether the association was independent of interval cardiac events, we also performed a sensitivity analysis in which we added interim cardiac events (myocardial infarction and AF) to the adjusted model 2 covariates, and found demonstrated no attenuation of the association (per SD decrease in LAFI, HR: 2.2, 95% CI: 1.7 to 2.9; $p < 0.001$).

The association did not vary by age, sex, the presence of obesity, prior history of HF, or AF (p for interaction > 0.10 for all). We found significant interactions between LAFI and the presence of hypertension ($p = 0.01$) and diabetes ($p < 0.001$). However, stratified analyses revealed the association was present among all subsets, and point estimates were similar in both strata (hypertension present, n = 185, HR: 3.0 per SD decrease in LAFI, 95% CI: 1.1 to 8.3 vs. hypertension absent, n = 670, HR: 2.0 per SD decrease in LAFI, 95% CI: 1.5 to 2.7; diabetes present, n = 239, HR:

Table 3 Unadjusted Association of Quartiles of Left Atrial Functional Index With Heart Failure Hospitalization

	Person-Time (Yrs)	Number of Events	Event Rate (per 1,000 Person-Yrs)	Unadjusted HR (95% CI)	p Value
Quartile IV (53.4–160 U)	1,503	8	5.3	—	—
Quartile III (40.8–53.4 U)	1,461	14	9.6	1.8 (0.8–4.3)	0.18
Quartile II (29.3–40.8 U)	1,424	26	18.3	3.4 (1.6–7.5)	0.001
Quartile I (0.5–29.2 U)	1,233	58	47.0	8.7 (4.2–18.2)	<0.001
Total	5,621	106	18.9		

*Log-rank $p < 0.001$.
CI = confidence interval; HR = hazard ratio.

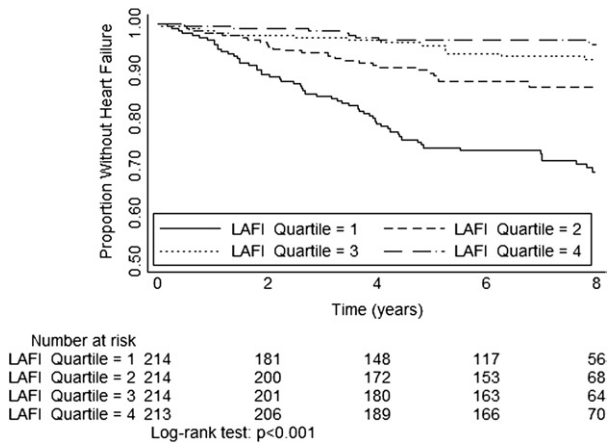

Figure 2 **Proportion Without HF Hospitalization, Stratified by Quartiles of LAFI**

Kaplan-Meier plot of time to heart failure (HF) hospitalization in subjects with stable coronary heart disease and left ventricular ejection fraction (LVEF) ≥50% at baseline, stratified by quartiles of the left atrial functional index (LAFI): **solid line** = quartile 1; **dashed line** = quartile 2; **dotted line** = quartile 3; **broken line** = quartile 4. The rate of heart failure hospitalization was highest in subjects in the lowest quartile of left atrial function, and lowest in subjects in the highest quartile of left atrial function (log-rank $p < 0.001$).

1.7 per SD decrease in LAFI, 95% CI: 1.2 to 2.4; and diabetes absent, n = 616, HR: 2.3 per SD decrease in LAFI, 95% CI: 1.6 to 3.4).

To better characterize the predictive ability of LAFI for incident HF, we also performed a subgroup analysis restricted to subjects with no prior history of HF (n = 724) and found results were similar to those of the entire cohort: subjects with LAFI in the lowest quartile had nearly 6 times the rate of incident HF hospitalization compared with subjects in the highest quartile (adjusted for model 1 covariates, HR: 5.8, 95% CI: 2.3 to 14.3; $p < 0.001$), and the rate of HF hospitalization was 80% greater per SD decrease in LAFI (HR: 1.8, 95% CI: 1.3 to 2.5, $p < 0.001$).

Given the marked preponderance of AF in the lowest quartile of LAFI, we also performed a subgroup analysis limited to only subjects without AF (n = 818), which demonstrated no difference compared with the entire cohort (adjusted for model 2 covariates, HR: 6.8, 95% CI: 3.0 to 15.0; $p < 0.001$), and the rate of HF hospitalization was 2-fold greater for every 1 SD decrease in LAFI (HR: 2.0, 95% CI: 1.5 to 2.7, $p < 0.001$).

The discrimination of LAFI for HF hospitalization was also superior to each of its individual components (unadjusted c-statistics, LAFI 0.73 vs. LVOT-VTI 0.60 [p for comparison <0.001], LA emptying fraction 0.65 [$p < 0.001$], and LAVI 0.69 [$p = 0.07$]). Cox models also revealed that LAFI provides prognostic value incremental to its component measures (chi-square likelihood ratio testing, $p < 0.001$ for all).

We also compared c-statistics to determine the incremental prognostic value of LAFI when used in conjunction with clinical risk factors and log NT-proBNP. The addition of LAFI to clinical risk factors was significantly more predictive of HF hospitalization than clinical risk factors alone (0.81 for clinical risk factors plus LAFI vs. 0.77 for clinical risk factors alone; $p < 0.001$), or clinical risk factors plus log NT-proBNP (0.85 for clinical risk factors plus log NT-proBNP plus LAFI vs. 0.81 for clinical risk factors plus log NT-proBNP alone; $p < 0.001$).

Discussion

In a cohort of 855 predominantly male out-patients with stable coronary artery disease and preserved baseline ejection fraction (≥50%), we found that LA dysfunction, as measured by LAFI, is associated with HF hospitalization. This association was independent of age, sex, race, traditional cardiovascular risk factors, heart rate, inducible ischemia, NT-proBNP, and other commonly used echocardiographic parameters (diastolic dysfunction, left atrial volume index,

Table 4 **Association of LAFI With Heart Failure Hospitalization, With Multivariate Adjustment**

	Quartile I Versus IV		Per SD Decrease in LAFI	
	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	p Value
Unadjusted	8.7 (4.2–18.2)	<0.001	2.6 (2.1–3.3)	<0.001
Adjusted models				
1*	7.6 (3.6–16.0)	<0.001	2.4 (1.9–3.0)	<0.001
2†	7.2 (3.2–16.2)	<0.001	2.0 (1.5–2.7)	<0.001
3‡	7.5 (2.8–19.8)	<0.001	2.0 (1.5–2.7)	<0.001
4§	3.4 (1.4–7.8)	0.005	1.4 (1.1–1.9)	0.02
5‖	3.2 (1.2–8.7)	0.02	1.5 (1.0–2.1)	0.05

*Adjusted for demographics (age, sex, white race). †Adjusted for model 1 covariates plus cardiovascular risk factors (tobacco use, prior revascularization, history of heart failure, atrial fibrillation, estimated glomerular filtration rate, low-density lipoprotein cholesterol), medication use (angiotensin-inhibitors, loop diuretics), and resting heart rate. ‡Adjusted for models 1 and 2 covariates plus baseline inducible ischemia. §Adjusted for models 1, 2, and 3 covariates plus log NT-proBNP. ‖Adjusted for models 1 through 4 covariates plus echocardiographic parameters (diastolic dysfunction, left atrial volume index, left ventricular ejection fraction, left ventricular mass index). The total number of participants in the final model was n = 769 due to missing data for race (n = 1), tobacco (n = 3), revascularization (n = 1), low-density lipoprotein (n = 22), history of heart failure (n = 4), diastolic dysfunction (n = 19), left ventricular mass index (n = 6), resting heart rate (n = 1), and NT-proBNP (n = 29).
CI = confidence interval; LAFI = left atrial functional index.

left ventricular ejection fraction, and left ventricular mass index).

Left atrial functional index. The LAFI is unique among means of characterizing the LA in that it combines expressions of atrial reservoir function (fractional change), adjusted atrial volume (LAVI), and stroke volume (VTI). For example, a patient with a large LA due to bradycardia will be correctly characterized by LAFI as having normal atrial function because both fractional change and VTI are increased.

The left atrium and HF. Prior studies have demonstrated a correlation between LA volume and diastolic dysfunction (27,28). Left atrial volume has also been shown to predict incident HF (29). Both rest and reserve LA function have been implicated in HF events in cross-sectional studies of subjects with HFpEF (14,30). Recent data have also found subjects with HFpEF to have increased atrial contribution to LV filling as a compensatory response to impaired early LV filling during exercise (31). Our demonstration of a longitudinal association between LA function and HF in subjects with preserved baseline EF complements these observations.

LA function in AF. Unlike other echocardiographic measures of LA function, the LAFI is unique in that it can be measured even in subjects with AF (16). Atrial fibrillation/flutter is a common comorbidity in subjects with HF; therefore, LAFI is an attractive parameter in this population. As expected, AF was far more common among subjects in the lowest quartile of LAFI compared with those in the highest 3 quartiles of LAFI. This is consistent with our previous finding that LAFI is low in subjects with AF and increases upon successful cardioversion to sinus rhythm (16). Although LAFI is lower in the setting of AF, we found that the association between LAFI and HF hospitalization was also independent of AF.

Other potential mechanisms of HFpEF. Although LA dysfunction is 1 potential mechanism of HFpEF, several other possible mediators have also been proposed, including inducible ischemia (32), elevated PASP (33), ventricular-arterial stiffening (34), and higher LV mass index (10,11,14). Our findings suggest that the association between LA dysfunction and HF hospitalization in subjects with preserved baseline EF is independent of these factors.

Clinical implications. Because the LA contributes up to 30% of stroke volume in healthy persons, its impairment may precipitate HF. Alternatively, LA dysfunction may simply be a consequence of other pathophysiologic mechanisms that cause HF. If causal, early efforts to prevent or arrest LA dysfunction may be beneficial for persons with high-risk clinical features. Notably, angiotensin inhibition, which had shown potential to reverse atrial remodeling in animal models (35), did not reduce mortality in clinical trials of subjects with HFpEF (8,9,36). However, other therapies that have shown promise for reversal of atrial remodeling, such as aldosterone antagonists (37)—currently being evaluated for the treatment of HFpEF in the ongoing TOPCAT (Treatment Of Preserved Cardiac function heart failure with an Aldosterone anTagonist) trial—restoration of sinus rhythm (38,39), or device therapies (40) could be considered. Regardless of whether improvement of LA function could affect outcomes, the LAFI provides prognostic value that is incremental to clinical risk factors and NT-proBNP, and therefore may be useful in risk stratification to identify patients with preserved baseline EF who are at high risk of HF hospitalization.

Study limitations. First, our cohort was composed of predominantly men, which may limit generalizability to women. However, testing for effect modification by sex revealed no difference in the association. Second, although we restricted our analysis to subjects who had a preserved EF at baseline, it is possible that EF or diastolic function may have declined in some subjects before HF hospitalization. However, adjustment for the presence of inducible ischemia at baseline and interim cardiac events (myocardial infarction and AF) did not attenuate the association. Third, electrocardiogram data at the time of HF failure presentation was not available; however, adjustment for interim development of AF based on electrocardiograms at year 5 demonstrated no change in the association. Fourth, the cutpoint of 50% for EF is widely used, but subjects in the lowest quartile probably include a proportion with established systolic dysfunction. However, further adjustment for EF demonstrated no significant change in the association. Fifth, we evaluated a single measure of resting LA function. Other echocardiographic measures of LA function, including Doppler tissue imaging, segmental atrial function assessment, strain, strain rate, and atrial response to exercise were not examined. Finally, some degree of over-fitting is present in the larger multivariate models; however, results were consistent with the more parsimonious models.

Conclusions

We found that LA dysfunction, as measured by the LAFI, is strongly and independently associated with HF hospitalization in patients with preserved baseline EF and stable coronary heart disease. This association remained independent even after adjustment for a wide range of clinical and echocardiographic covariates, and the prognostic value of the LAFI was incremental to clinical risk factors and NT-proBNP. The LAFI may be useful for HF risk stratification, and LA dysfunction may be a potential therapeutic target.

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Key Words: coronary heart disease ■ heart failure hospitalization ■ heart failure with preserved ejection fraction ■ left atrial function ■ left atrial functional index.